AMENDMENTS TO SPECIFICATION

Please amend the specification at pages 7-8, paragraph [0016] as follow:

Further, it was also identified that similar functions exist in the TCL1B and MTCP1 (human) having the similar functions to those of TCL1, and found that the cell growth associated with Akt activation inhibits at the positions of an amino acid residue8-22 in amino acid sequence of TCL1B (human) and of an amino acid residue5-19 in amino acid sequence of MTCP1 (human); and then the present invention was completed. Furthermore, in the present invention, it was also identified that the cell growth associated with Akt activation was inhibited at the positions of an amino acid residue9-24 in amino acid sequence of mouse TCL1 and of an amino acid residue9-24 in amino acid sequence of rat TCL1. Polypeptide in the present invention competitively inhibits the binding of ~~phsphoinositide~~ phosphoinositide (phosphatidylinositol) to Akt.

Please amend the specification at page 11, paragraph [0023] as follow:

The present invention still further relates to (11) a specific inhibitor of Akt activity, wherein the polypeptide according to "1" or "2" is an active ingredient; (12) the specific inhibitor of Akt activity according to "11", wherein the polypeptid is a sequence of an amino acid residue10-24 of an amino acid sequence for human TCL1 protein; (13) the specific inhibitor of Akt activity according to "11", wherein the polypeptid is a sequence of an amino acid residue8-22 of an amino acid sequence for human TCL1B protein; (14) the specific inhibitor of Akt activity according to "11", wherein the polypeptid is a sequence of an amino acid residue5-19 of an amino acid sequence for human MTP1 protein; (15) the specific inhibitor of Akt activity according to "11", wherein the polypeptid is a sequence of an amino acid residue9-24 of an

amino acid sequence for mouse TCL1 protein; (16) the specific inhibitor of Akt activity according to "11", wherein the polypeptid is a sequence of an amino acid residue9-24 of an amino acid sequence for rat MTP1 protein; and (17) the specific inhibitor of Akt activity according to any one of "11"-"16", wherein specific inhibition of Akt activity is the inhibition of binding of ~~phsphoinositide~~ phosphoinositide to Akt.

Please amend the specification at page 24, paragraph [0044] as follow:

[TCL1 (human) amino acid random mutation library screening for identification of the Akt-TCL1 binding site]

(Materials and Methods)

1. TCL1 library

A full length of human TCL1 in pGAD424 (Clontech) was amplified by PCR with the use of a primer comprising 5'-CCACCAAACCCAAAAAAAGAGATCGAATTCATG (SEQ ID NO: 11) and 5'-ATTCATAGATCTCTGCAGGTCGACGGATCCTCA (SEQ ID NO: 12), and a random TCL1 amino acid library was produced.

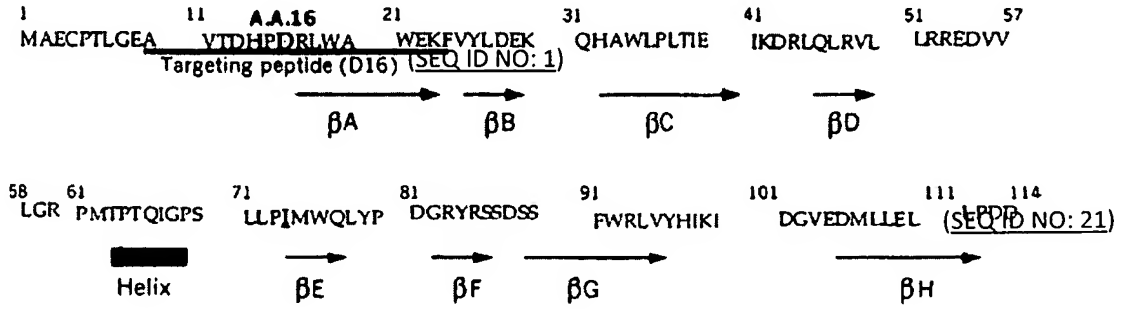
Please amend the specification at page 25, paragraph [0046] as follow:

Primers used are as follows (mutated codons are shown in lower-case letters): 5'-ATG GCC GAG TGC CCG ACA CTC GGG GAG GCA GTC ACC GAC CAC CCG GGC CGC CTG TGG GCC (SEQ ID NO: 13) for D16G; 5'-GTG TAT TTG GAC GAG ATG CAG CAC GCC TGG CTG (SEQ ID NO: 14) for K30M; 5'-G ATA AAG GAT AGG TTA CGG TTA CGG GTG CTC TTG (SEQ ID NO: 15) for Q46R; 5'-CCA AGC CTG CTG CCT GTC ATG TGG CAG CTC TAC (SEQ ID NO: 16) for 174V; 5'-ATC ATC GGA TCC TCA GTC ATC TGG CAG CAG CTC GAG AAG CAC GTC CTC C (SEQ ID NO: 17) for M106V; 5'-CAG CAC GCC TGG CTG GCC GCG GCC ATC GAG ATA AAG GAT (SEQ ID NO: 18) and a

reverse complementary sequence for 36-38A; and 5'-GCC TGG CTG GCC TTA ATC GAG ATA (SEQ ID NO: 19) and a reverse complementary sequence for 36A/38Δ. Mutated positions of an amino acid-substituted mutant form of TCL1 (D16G, K30M, Q46R, 174V, M106V, 36-38A, or 36A/38Δ) are shown in figure 1.

Please amend the specification at page 29, paragraph [0055], table 1 as follow:

[Table 1]



Please amend the specification at pages 29-30, paragraph [0057], table 2 as follow:

[Table 2]

Targeting peptides design

	NH2-TAT (YGRKKRRQRRR)- Flag(DYKDDDDK)- Target Peptides -COOH	(SEQ ID NO: 23)
10/24 peptide	NH2-YGRKKRRQRRR- DYKDDDDK- AVTDHPDRLWAWEKF -COOH	(SEQ ID NO: 24)
Control Peptide	NH2-YGRKKRRQRRR- DYKDDDDK- SQAVHAAHEI -COOH	(SEQ ID NO: 25)

Please amend the specification at page 30, paragraph [0058] as follow:

[Assay for 10/24 peptide of TCL1]

1. Cell growth test by using MTT assay

Cell growth test was performed by using MTT assay. That is, in experiments of cell growth by using WST-8 reagent [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-

disulfophenyl)-2H-tetrazolium, monosodium salt] (347-07621, Dojin, Kumamoto, Japan) assay, it was identified that amino acid residue sequence 10-24 peptide (NH2- - AVTDHPDRLWAWEKF -COOH) (SEQ ID NO: 1) of this TLC1 oncogene specifically inhibits cell growth associated with AKT activation (Fig. 6).

Please amend the specification at pages 30-31, paragraph [0060] as follow:

2. Binding test by co-immunoprecipitation assay

To examine the cause of inhibition of the specific cell growth of 10/24 peptide, by using co-immunoprecipitation assay, it was identified that 10/24 peptide specifically binds to Akt kinase (Fig. 7). In this method, AKT kinase was overexpressed in human 293 cells, and the harvested cell lysates was incubated with 10/24 peptide (NH2- - AVTDHPDRLWAWEKF - COOH) (SEQ ID NO: 1) for around 2 hours. Further, the treated cell lysates were added agarose beads bound to the specific antibody against an epitope that was fused with Akt, and co-incubated for 2-3 hours. Then, molecules adhered in the cell lysates were immunoprecipitated with agarose beads bound to this antibody, and examined the binding to Akt kinase by using western blotting with specific antibody.

Please amend the specification at page 30, paragraph [0058] as follow:

2. Lipid-protein pull down assay

Lipid-protein pull down assay was performed for 10/24 peptide of TCL1.

Method:

Lipid-protein pull down assay was performed by using PIP Beads (PI (3,4,5) P3 Echelon Bioscience Incorporated). 10/24 NH2- AVTDHPDRLWAWEKF -COOH (SEQ ID NO: 1), and βC NH2- EKQHAWLPLTIE -COOH (SEQ ID NO: 22) as a control, were used. After treatment

for 2 hours at 4°C by using 50ng of AKT kinase (unactivated, Upstate Biotechnology, #14-279), 25 μl of PIP Beads (PI (3,4,5) P3 Echelon Bioscience Incorporated) was added, then washed with fluid containing (10 mM Hepes, pH7.4, 0.25% NP-40、140mM NaCl), and western blotting was performed by using Akt antibody (Cell Signaling) (Fig. 8). In three lanes from the left in the figure, the bindings to AKT were inhibited in a dose-dependent manner at 1-400 μM, while control peptides in right lanes in the figure did not inhibit at all. From these results, it was identified that the peptide (NH2- - AVTDHPDRLWAWEKF -COOH) (SEQ ID NO: 1) competitively inhibits the bindings of Phosphoinositide (PI (3,4,5) P3) to Akt kinase. Thus, this is considered to be the inhibition mechanism for Akt activation.

Please amend the specification at pages 32-33, paragraph [0063] as follow:
[Inhibition effect test for Akt activation by Akt kinase assay with the use of GSK (Glycogen Synthesis Kinase 3) as substrate]

It has been known that Akt promotes phosphorylation of GSK (Glycogen Synthesis Kinase 3).

With the use of the GSK as substrate Akt kinase assay was performed, and inhibition test for Akt activation with 10/24 peptide was performed.

Method:

In vitro Akt kinase assay was performed by using kit (Cell Signaling, #9840). Recombinant Akt protein extracted from mammalian cells was mixed with 200 μM concentrations of peptide, and reacted for 2 hours. Phosphorylation was performed for 4 minites at 30°C. After analyzing the reaction mixture on SDS gels, GSK phosphorylation was determined by western blotting. The results are shown in figure 8. As shown in the figure 8, the

10/24 peptide was effectively inhibited the phosphorylation potency for GSK peptide of Akt (three lanes from the left in the figure show the inhibition of GSK phosphorylation diluting the black bands). The similar inhibition effect on Akt kinase activity was also identified by using peptide (NH2- VTDHPDRLWAWEK -RRR- VTDHPDRLWAWEK -COOH) (SEQ ID NO: 20) having repetitive sequence of 11-23 from 10-24(AVTDHPDRLWAWEKF) (SEQ ID NO: 1).

Please amend the specification at pages 35-36, paragraph [0067] as follow:

[Induction of apoptosis and anti-tumor effect by 10/24 peptide]

The effect on apoptosis of 10/24 peptide was examined with the use of human T cell leukemia cells (T4).

Method:

10/24 peptide (NH2- - AVTDHPDRLWAWEKF -COOH) (SEQ ID NO: 1) was pre-treated at 0-30 μM concentrations with the use of T4 cell lines without stimulation, 48 hours later stained with propidium iodide, and the apoptosis was determined by FACS(Beckton Dickinson). Further, to identify the AKT dependency of the anti-tumor effect, myr-AKT (constitutively activated AKT) was overexpressed. The results are shown in figure 11. As shown in the figure, 10/24 peptide was identified to enhance apoptosis, compared with control peptide. Similar tendency to enhance the apoptosis was also identified during the induction of apoptosis by dexamethasone. As a result of myr-AKT overexpression, apoptosis was inhibited (Δ in Fig. 11), and it was identified that 10/24 peptide achieves the effect in AKT dependent manner.